

Clinical Applications: Neurodegenerative Disorders

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Parkinson's disease (PD) and Alzheimer's disease (AD) are the two most common neurodegenerative disorders. Multiple sclerosis (MS) is the most common demyelinating disorder. Although there are strong inflammatory components to multiple sclerosis, it is clear that the disease also has a strong neurodegenerative component. Combined these three disease processes affect more than 6 million Americans in countless more people around the world. The cost related to care and treatment for these patients are staggering both in terms of human suffering and the financial burdens on the patient and families as well as national health care systems. In the US alone, some estimates suggest that over \$100 billion is spent yearly in terms of direct and indirect health-care costs. The total amount spent on neurodegenerative processes, particularly for AD and PD, is expected to rise given the aging demographic in the US and other countries.

AD and PD have been studied extensively using a variety of imaging techniques. Conventional MR imaging has played a primary role in excluding other neurologic abnormalities. Multiple sclerosis has been extensively studied using conventional MR imaging techniques. Unlike AD and PD, conventional MR imaging plays an important role in the diagnosis of MS. Newer imaging techniques such as diffusion tensor imaging and functional MRI offer the potential for improved diagnosis, better understanding of the underlying mechanisms, improved disease monitoring and guidance of therapy PD, AD, and MS

The majority of MR imaging research directed towards Alzheimer's disease has focused on morphologic measurements. There's a large body of information documenting morphologic changes related to Alzheimer's disease, particularly, findings of hippocampal and cortical atrophy. A multitude of quantitative methodologies have been proposed for assessment of atrophy. Overall findings suggest that morphologic measurements are useful for the diagnosis of AD, sensitive to early changes in mild cognitive impairment and useful for monitoring disease progression. (1-8)

More recently, cognitive impairments associated with Alzheimer's disease have been studied using functional MRI. There are significant underlying issues related to task performance, evaluation of functional activation in the face of atrophy and age-related changes in blood flow and vascular coupling to be considered in studying Alzheimer's patients. Despite these considerations, an increasing body of literature has accumulated over the last several years demonstrating fMRI activation changes in Alzheimer's disease utilizing a variety of tasks including memory, verbal and semantic tasks. Findings suggest decreased activation in the hippocampal regions of patients with mild cognitive impairment and Alzheimer's disease during performance of memory tasks. Early fMRI results from studies suggest that they are promising for evaluation of patients at risk for AD, patients with minimal cognitive impairment and those with AD. Interestingly, fMRI studies have also suggested changes in activation patterns in response to pharmacologic therapy. More recently, new functional techniques such as functional connectivity have demonstrated changes in brain networks in subjects with Alzheimer's disease in comparison to age matched controls. In contrast to functional MRI evaluations, there've been relatively few studies of DTI imaging in Alzheimer's disease. Early findings suggest that there

may be some differences in regional fractional anisotropy in an Alzheimer's subjects in comparison to age matched healthy controls. (1) (9-32)

Parkinson's disease has been studying using morphologic measurements as well and conventional MRI. Some authors have suggested significant increases in the degree of iron deposition within the substantia nigra in patients with PD in comparison to controls. Unfortunately, this measurement is relatively difficult to make and demonstrates overlap with normal subjects. The primary role of conventional MRI in PD has been to exclude other pathologic processes. Importantly, conventional MRI may have a role in distinguishing Parkinson's disease from other parkinsonian syndromes such as multisystem atrophy and progressive supranuclear palsy. Additionally studies have been performed looking at atrophy and cognitive function in PD. (33-42)

More recently, investigators have used functional MRI to further study Parkinson's disease. PD has been studied using a variety of paradigms including memory, learning, language and motor tasks. Investigators have shown changes in both the degree and position of activation in PD patients in comparison to controls. The most consistent finding during motor fMRI is a decrease in the extent of activation within the rostral portion of the supplementary motor area. Cognitive studies have shown changes within the lateral prefrontal cortices during performance of cognitive tasks in patients with PD. Interestingly, cognitive tasks which utilize the striatal regions tend to show greater differences between controls and subjects with PD. Tasks not involving the striatum tend to be relatively spared. Additionally, functional MRI changes have also been identified in relationship to medical therapies for Parkinson's disease. Functional MRI tasks performed before and after levodopa therapy demonstrate recovery of activation within the supplementary motor area. The effect on activation within the primary motor cortices varies between studies. Interestingly, the effect of levodopa appears to be different in cognitive versus motor tasks. Although motor task tended to show greater activation during levodopa therapy, performance of working memory task demonstrated decreased activation in response to levodopa therapy. This may reflect some increased efficiency for working memory with levodopa therapy. Note evaluation of the effects of drug therapy on fMRI results need to be carefully considered in light of differential task performance between the on versus off therapy conditions. The findings in these studies show promise for developing potential functional MRI indices to better understand the mechanisms, follow disease progression and better understand treatment effects in PD (43-55)

Surgical therapies both lesional and for placement of deep brain stimulator's have become an integral part of Parkinson's disease therapy. Imaging has played a critical role in the development of these therapies. Both preoperative and postoperative imaging techniques have been developed to optimize both lesional and deep brain stimulator therapies. Recently, several investigators have applied functional MRI to the evaluation of deep brain stimulator's. DBS placed in the subthalamic nucleus appears to produce a consistent pattern of activation in the ipsilateral basal ganglia and thalamus. Functional MRI may provide confirmation for DBS function and appropriate placement in the future. (56-63)

DTI imaging has not been used extensively for assessment of Parkinson's disease. It may, however, have a role to play in the future in developing appropriate planning for the placement of deep brain stimulator's. Several authors have suggested that deep brain stimulator functioned can be modeled using information from DTI images. Modeling of the electric fields generated by DBS may be used in the future in order to optimize therapy. (63)

Multiple sclerosis is commonly thought of as a demyelinating disease process. Recently, there has been increasing evidence that MS has a strong neurodegenerative component. MS lesions clearly produce axonal transection and subsequent axonal loss. These changes may be the underlying substrate for the observed generalized atrophy seen in MS. Further evidence for axonal loss in the generation comes from MR spectroscopy data demonstrating decreased NAA in MS patients. Additionally, MS therapies have largely focused on anti-inflammatory medications. Even the best of these medications only partially alter progression/course of the disease. All of these lines of evidence suggest the presence of a strong neurodegenerative component to MS. (64-79)

MS has been studied extensively using conventional MRI. Conventional MRI is integral to the diagnosis of MS. Despite the extensive use of conventional MR imaging in multiple sclerosis, there is a relatively poor correlation between conventional MR measures of MS lesions burden in functional disability. This may relate to several potential drawbacks of conventional MR imaging. Conventional techniques tend to be insensitive to changes in normal appearing white matter, are typically whole brain imaging techniques which are compared to relatively pathway specific measures of disability and do not take into account the potential cortical reorganization and/or adaptation suggested by recent functional MRI studies. (80-85)

MS has been studied by multiple investigators using functional MRI. The most consistent finding of these investigations has been an increase in the size of the regions of cortical activation in comparison to control subjects and in many cases the appearance of activation in brain regions not seen in control subjects. This finding has been consistent across a variety of motor and cognitive tasks. Findings suggest some element of cortical adaptation and or reorganization in response to multiple sclerosis. The most typical finding has been a relative spreading out of activation to adjacent brain regions in comparison to control subjects. In other words, a larger area of activation is present. The more interesting and intriguing findings have been the appearance of activation in brain regions which do not typically serve the particular function being tested. The underlying mechanism behind the changes in activation in MS patients in comparison to controls has been attributed to a variety of processes including cortical reorganization, cortical adaptation, compensatory cortical change, changes related to loss of inhibition and unmasking of underlying brain function. (86-111)

Although the mechanism for changes in cortical activation in MS patients is not well understood, the degree of change appears to be correlated to disease burden. fMRI changes have been seen in all stages and subtypes of MS including clinically isolated syndrome suggestive of MS, relapsing-remitting MS, primary progressive MS and secondary progressive multiple sclerosis. As would be expected, pathway specific measures of lesion burden correlate well with changes in the degree of functional activation. Specifically, increasing lesion burden within the motor pathway produces increased motor cortex activation. One study demonstrated a single patient with new onset hemiparesis during a relapse of multiple sclerosis using both spectroscopy and functional MRI. They showed that motor pathway NAA, a marker of neuronal integrity, correlated inversely with the size of cortical activity associated with motor movement. Specifically, during the early phases of the patients relapse NAA values were low and there was a large area of cortical activation. During the resolution of symptoms the recovery of NAA values was associated with a decrease in the size of the degree of cortical activation. This finding suggests a strong correlation between pathway specific lesion burden and activation within a specific portion of cortex suggesting that fMRI may be sensitive to acute and ongoing changes in MS. (86-112)

Results from these early studies using fMRI in multiple sclerosis suggest the possibility that MS subjects may retain or recover function in the face of ongoing disease progression through cortical

adaptation/reorganization. These findings suggest that despite ongoing demyelination and neurodegeneration MS patients are able to form and potentially myelinate new functional pathways. Further, many of these new pathways may be in relatively unexpected brain regions which are thought to serve other functions.

Similar to other neurodegenerative processes careful consideration for potential confounding factors in fMRI need to be considered for evaluation of MS. Specifically, careful assessment of task performance and evaluation of patient motion are required. Additionally, as recent studies have demonstrated altered perfusion in MS careful consideration of potential confounding factors related to abnormal blood flow/neurovascular coupling need to be considered. Despite these potential caveats fMRI may provide a useful tool to understand the ongoing disease process in MS.

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